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FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 16:49:32 ON 10 MAY 2005
L1         88187 S ADENOVIR?
L2        295203 S APOPTOSIS
L3         10066 S FASL
L4       3966166 S CANCER OR TUMOR OR NEOPLASM? OR METASTASIS OR ANAPLAST?
L5        318959 S PROMOTER
L6         81522 S CONDITIONAL OR "TISSUE SPECIFIC" OR INDUBIBLE
L7        112709 S TETRACYCLINE OR DOXYCYCLINE
L8        413339 S GLUCOCORTICOID OR ESTROGEN OR ANDROGEN OR PROGESTRONE
L9         37565 S NORRIS?/AU OR DONG?/AU
L10        17681 S "DEATH DOMAIN" OR CD95 OR APO1 OR APO-1
L11          470 S L5 (2W) L6
L12            0 S L1 AND L3 AND L11
L13          351 S L1 AND L3
L14          123 S L13 NOT PY>=2001
L15           45 S L14 NOT PY>=1999
L16           25 DUP REM L15 (20 DUPLICATES REMOVED)
L17            0 S L11 AND L3
L18            0 S L11 AND L10
L19            9 S L11 AND L1
L20            5 DUP REM L19 (4 DUPLICATES REMOVED)
L21            2 S L20 NOT PY>=1999
L22          237 S L4 AND L1 AND L2 AND L10
L23           39 S L22 NOT PY>=1999
L24           21 DUP REM L23 (18 DUPLICATES REMOVED)
L25         1882 S L5 (S) L7
L26            0 S L24 AND L25
L27            0 S L24 AND L6
L28            0 S L24 AND L9
L29           73 S L3 AND L9
L30            7 S L29 NOT PY>=1999
L31            3 DUP REM L30 (4 DUPLICATES REMOVED)
L32         3831 S EXPRESSION (S) FASL
L33           18 S L32 AND L6
L34            0 S L33 NOT PY>=1999
L35            8 DUP REM L33 (10 DUPLICATES REMOVED)

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L35 ANSWER 1 OF 8 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2003587515 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14668794
TITLE: CD95/Fas signaling in human melanoma cells: **conditional expression** of CD95L/ **FasL** overcomes the intrinsic apoptosis resistance of malignant melanoma and inhibits growth and progression of human melanoma xenotransplants.
AUTHOR: Eberle Jurgen; Fecker Lothar F; Hossini Amir M; Wieder Thomas; Daniel Peter T; Orfanos Constantin E; Geilen Christoph C
CORPORATE SOURCE: Department of Dermatology, Charite-Universitatsmedizin Berlin, Campus Benjamin Franklin, 14195 Berlin, Germany.. eberle@medizin.fu-berlin.de
SOURCE: Oncogene, (2003 Dec 11) 22 (57) 9131-41. Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 20031216
Last Updated on STN: 20040108
Entered Medline: 20040107

AB The significance of CD95/Fas ligand expression by melanoma cells has remained a controversial matter in recent years. On the other hand, CD95 activation may represent a powerful tool for eliminating tumor cells. Here, we demonstrate expression of CD95 in 15/17 human melanoma cell lines analysed, but complete lack of CD95 ligand (CD95L). Overexpression of CD95 in a tetracycline-inducible expression system enhanced melanoma cell sensitivity to CD95 ligation but was unable to trigger apoptosis by itself. In clear contrast, all melanoma cells tested responded with increased apoptosis to **conditional** expression of CD95L (2-10-fold), both after transient and after stable transfection. Activation of caspase-8, Bid cleavage, cytochrome c release and caspase-3 activation followed after CD95L induction indicating a functional CD95-signaling cascade. CD95L was also able to enhance the proapoptotic effect of chemotherapeutics applied in parallel. Nude mouse experiments revealed that tumorigenicity was lost when melanoma xenografts were triggered to express CD95L. In addition, further progression of pre-existing melanomas was inhibited and even regression was seen after induction of CD95L expression. Due to these data, transfection of CD95L proofs as a highly efficient tool against melanoma cells in vitro and in vivo, and targeted expression of CD95L may thus represent a suitable strategy for melanoma therapy.

L35 ANSWER 2 OF 8 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:258445 BIOSIS
DOCUMENT NUMBER: PREV200100258445
TITLE: Identifying the Fas-expressing target in autoimmune demyelinating disease.
AUTHOR(S): Gimenez, Maryann T. [Reprint author]; Russell, John H. [Reprint author]
CORPORATE SOURCE: Washington University School of Medicine, 660 S. Euclid Avenue, St. Louis, MO, 63110, USA
SOURCE: FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A1064. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001. Orlando, Florida, USA. March 31-April 04, 2001.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 30 May 2001
Last Updated on STN: 19 Feb 2002

AB Fas is a type one membrane protein that has the ability to induce apoptosis in Fas-bearing cells when it is bound to Fas ligand (FasL). Fas

and FasL have been implicated in both prevention and pathogenesis of autoimmune disease. A functional mutation in either Fas or FasL, as is seen in lpr or gld mice, respectively, results in an autoimmune lymphoproliferative disease, which mimicks the disease systemic lupus erythematosus (SLE). However, functional **expression** of Fas and **FasL** has been linked to the pathogenesis of organ specific diseases, such as autoimmune hepatitis, diabetes, thyroid disease and multiple sclerosis. We have previously demonstrated that the lpr and gld mutations ameliorate active induction of experimental autoimmune encephalomyelitis (EAE) with MBP in B10.PL mice. Furthermore, through adoptive transfer experiments we have demonstrated that **FasL expression** on the encephalitogenic T cell and Fas **expression** on a target cell in the CNS is necessary for initiation of EAE in B10.PL mice. The identification of this Fas-expressing target cell has, thus far, eluded us. In order to determine which cell in the CNS is a target for Fas-induced apoptosis, we have created a construct that will knockout Fas expression, via the recombination of two loxP sites that flank the first exon of Fas, only in cells that express the cre recombinase. In addition, GFP will be expressed under the Fas promoter following cremediated excision of exon 1. With our Fas **conditional** knockout, we will be able to test which specific cell in the CNS, for example oligodendrocytes or neurons, is the target for Fas-mediated apoptosis.

L35 ANSWER 3 OF 8 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2001324613 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11285454
TITLE: Is pancreas development abnormal in the non-obese diabetic mouse, a spontaneous model of type I diabetes?.
AUTHOR: Homo-Delarche F
CORPORATE SOURCE: CNRS UMR 8603, Universite Paris V, Hopital Necker, 161, rue de Sevres, 55015 Paris, France.. fhomodel@wanadoo.fr
SOURCE: Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas / Sociedade Brasileira de Biofisica ... [et al.], (2001 Apr) 34 (4) 437-47. Ref: 60
Journal code: 8112917. ISSN: 0100-879X.
PUB. COUNTRY: Brazil
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010611
Last Updated on STN: 20010611
Entered Medline: 20010607

AB Despite extensive genetic and immunological research, the complex etiology and pathogenesis of type I diabetes remains unresolved. During the last few years, our attention has been focused on factors such as abnormalities of islet function and/or microenvironment, that could interact with immune partners in the spontaneous model of the disease, the non-obese diabetic (NOD) mouse. Intriguingly, the first anomalies that we noted in NOD mice, compared to control strains, are already present at birth and consist of 1) higher numbers of paradoxically hyperactive beta cells, assessed by in situ preproinsulin II **expression**; 2) high percentages of immature islets, representing islet neogenesis related to neonatal beta-cell hyperactivity and suggestive of in utero beta-cell stimulation; 3) elevated levels of some types of antigen-presenting cells and **FasL+** cells, and 4) abnormalities of extracellular matrix (ECM) protein **expression**. However, the colocalization in all control mouse strains studied of fibroblast-like cells (anti-TR-7 labeling), some ECM proteins (particularly, fibronectin and collagen I), antigen-presenting cells and a few FasL+ cells at the periphery of islets undergoing neogenesis suggests that remodeling phenomena that normally take place during postnatal pancreas development could be disturbed in NOD mice. These data show that from birth onwards there is an intricate relationship between endocrine and immune events in the NOD mouse. They also suggest that **tissue-specific** autoimmune reactions

could arise from developmental phenomena taking place during fetal life in which ECM-immune cell interaction(s) may play a key role.

L35 ANSWER 4 OF 8 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2001663943 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11708878
TITLE: A complex adenovirus vector that delivers **FASL** -GFP with combined prostate-specific and tetracycline-regulated **expression**.
AUTHOR: Rubinchik S; Wang D; Yu H; Fan F; Luo M; Norris J S; Dong J Y
CORPORATE SOURCE: Department of Microbiology and Immunology, Medical University of South Carolina, Charlestown, SC 29403, USA.
SOURCE: Molecular therapy : journal of the American Society of Gene Therapy, (2001 Nov) 4 (5) 416-26.
Journal code: 100890581. ISSN: 1525-0016.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20011119
Last Updated on STN: 20020308
Entered Medline: 20020307
AB Cell-type-restricted transgene expression delivered by adenovirus vectors is highly desirable for gene therapy of cancer, as it can limit cytotoxic gene expression to tumor cells. However, many tumor- and **tissue -specific** promoters are weaker than the constitutively active promoters and are thus less effective. To combine cell-type specificity with high-level regulated transgene expression, we have developed a complex adenoviral vector. We have placed the tetracycline transactivator gene under the control of a prostate-specific ARR2PB promoter, and a mouse Tnfsf6 (encoding FASL)-GFP fusion gene under the control of the tetracycline responsive promoter. We have incorporated both expression cassettes into a single construct. We show that **FASL**-GFP **expression** from this vector is essentially restricted to prostate cancer cells, in which it can be regulated by doxycycline. Higher levels of prostate-specific **FASL**-GFP **expression** were generated by this approach than by driving the **FASL**-GFP **expression** directly with ARR2PB. More **FASL**-GFP **expression** correlated with greater induction of apoptosis in prostate cancer LNCaP cells. Mouse studies confirmed that systemic delivery of both the prostate-specific and the prostate-specific/tet-regulated vectors was well tolerated at doses that were lethal for FASL-GFP vector with CMV promoter. This strategy should be able to improve the safety and efficacy of cancer gene therapy using other cytotoxic genes as well.

L35 ANSWER 5 OF 8 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2000253201 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10791994
TITLE: Proinflammatory consequences of transgenic fas ligand expression in the heart.
AUTHOR: Nelson D P; Setser E; Hall D G; Schwartz S M; Hewitt T; Klevitsky R; Osinska H; Bellgrau D; Duke R C; Robbins J
CORPORATE SOURCE: Division of Molecular Cardiovascular Biology, and. Division of Cardiology, Department of Pediatrics, The Children's Hospital Research Foundation, Cincinnati, Ohio, USA.
CONTRACT NUMBER: AI40394 (NIAID)
HL41496 (NHLBI)
HL56370 (NHLBI)
+
SOURCE: Journal of clinical investigation, (2000 May) 105 (9) 1199-208.
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000606
Last Updated on STN: 20000606
Entered Medline: 20000525

AB **Expression** of Fas ligand (**FasL**) renders certain tissues immune privileged, but its **expression** in other tissues can result in severe neutrophil infiltration and tissue destruction. The consequences of enforced **FasL expression** in striated muscle is particularly controversial. To create a stable reproducible pattern of cardiomyocyte-specific **FasL expression**, transgenic (Tg) mice were generated that express murine **FasL** specifically in the heart, where it is not normally expressed. Tg animals are healthy and indistinguishable from nontransgenic littermates. **FasL expression** in the heart does result in mild leukocyte infiltration, but despite coexpression of Fas and **FasL** in Tg hearts, neither myocardial tissue apoptosis nor necrosis accompanies the leukocyte infiltration. Instead of tissue destruction, **FasL** Tg hearts develop mild interstitial fibrosis, functional changes, and cardiac hypertrophy, with corresponding molecular changes in gene **expression**. Induced expression of the cytokines TNF-alpha, IL-1beta, IL-6, and TGF-beta accompanies these proinflammatory changes. The histologic, functional, and molecular proinflammatory consequences of cardiac **FasL expression** are transgene-dose dependent. Thus, coexpression of Fas and FasL in the heart results in leukocyte infiltration and hypertrophy, but without the severe tissue destruction observed in other examples of FasL-directed proinflammation. The data suggest that the **FasL expression** level and other **tissue-specific** microenvironmental factors can modulate the proinflammatory consequences of **FasL**.

L35 ANSWER 6 OF 8 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2001191950 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11200813
TITLE: Enhanced expression of Fas-associated proteins in decidual and trophoblastic tissues in pregnancy-induced hypertension.
AUTHOR: Koenig J M; Chegini N
CORPORATE SOURCE: Department of Pediatrics, University of Florida, Gainesville, USA.. koenijm@peds.ufl.edu
SOURCE: American journal of reproductive immunology (New York, N.Y. : 1989), (2000 Dec) 44 (6) 347-9.
Journal code: 8912860. ISSN: 1046-7408.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010410
Last Updated on STN: 20010410
Entered Medline: 20010405

AB PROBLEM: To determine if feto-placental tissues from gestations complicated by pregnancy-induced hypertension (PIH) have altered expression of Fas-associated proteins. METHOD OF STUDY: The expression of several Fas-related proteins was determined in fetal membranes, decidua, and placentas obtained from PIH-affected (n = 12, age range 32-36 weeks) and normal (n = 6, age range 37-41 weeks) gestations. Paraffin-embedded tissue sections were stained with specific monoclonal antibodies to Fas, Fas ligand (FasL), caspase-3, and bax. RESULTS: We observed greater **expression** of Fas and **FasL** in amnion and decidua from PIH-affected gestations than in normal controls. Intense staining was observed only in the perivascular endothelium (caspase-3) and in decidual cells (bax) from PIH gestations. CONCLUSION: Differential **expression** of Fas-related proteins in fetal membranes, decidua, and placentas from PIH-affected gestations is consistent with increased apoptosis, and suggests activation of the Fas/**FasL** pathway in a **tissue-specific** manner.

L35 ANSWER 7 OF 8 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2000297048 MEDLINE

DOCUMENT NUMBER: PubMed ID: 10837061
TITLE: Glucocorticoids in T cell development and function*.
AUTHOR: Ashwell J D; Lu F W; Vacchio M S
CORPORATE SOURCE: Laboratory of Immune Cell Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.. jda@Box-j.nih.gov
SOURCE: Annual review of immunology, (2000) 18 309-45. Ref: 220
Journal code: 8309206. ISSN: 0732-0582.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000720
Last Updated on STN: 20000720
Entered Medline: 20000712

AB Glucocorticoids are small lipophilic compounds that mediate their many biological effects by binding an intracellular receptor (GR) that, in turn, translocates to the nucleus and directly or indirectly regulates gene transcription. Perhaps the most recognized biologic effect of glucocorticoids on peripheral T cells is immunosuppression, which is due to inhibition of expression of a wide variety of activationinduced gene products. Glucocorticoids have also been implicated in Th lineage development (favoring the generation of Th2 cells) and, by virtue of their downregulation of **fasL expression**, the inhibition of activation-induced T cell apoptosis. Glucocorticoids are also potent inducers of apoptosis, and even glucocorticoid concentrations achieved during a stress response can cause the death of CD4(+)CD8(+)thymocytes. Perhaps surprisingly, thymic epithelial cells produce glucocorticoids, and based upon in vitro and in vivo studies of T cell development it has been proposed that these locally produced glucocorticoids participate in antigen-specific thymocyte development by inhibiting activation-induced gene transcription and thus increasing the TCR signaling thresholds required to promote positive and negative selection. It is anticipated that studies in animals with **tissue-specific** GR-deficiency will further elucide how glucocorticoids affect T cell development and function.

L35 ANSWER 8 OF 8 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2000016595 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10548879
TITLE: Apoptosis and cell death in the endocrine system.
AUTHOR: Mountz J D; Zhang H G; Hsu H C; Fleck M; Wu J; al-Maini M H; Zhou T
CORPORATE SOURCE: Department of Medicine, University of Alabama, Birmingham 35294-0007, USA.
CONTRACT NUMBER: CA13148 (NCI)
NO-1 AR-62224 (NIAMS)
SOURCE: Recent progress in hormone research, (1999) 54 235-68; discussion 269. Ref: 175
Journal code: 0404471. ISSN: 0079-9963.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991208

AB Inflammatory diseases of the endocrine system--such as thyroiditis, diabetes, and Graves' disease--are considered to be autoimmune in origin. More recently, these and other autoimmune diseases have been associated with defects in Fas apoptosis. The mutation of the Fas or Fas ligand (FasL) has been observed in a minority of patients with autoimmune disease. However, dysfunction of the Fas apoptosis signaling pathway or production of soluble factors, including sFas and sFasL, may be more prevalent. Certain endocrine tissues, such as the testes, are immune

privilege sites. Defects in Fas and **FasL expression** in immune privilege sites can trigger an inflammatory response. Other factors that trigger inflammatory diseases of the thyroid or islets may be loss of self tolerance, leading to an autoimmune response. An infectious trigger or other environmental agent can initiate organ damage, leading to release of new antigens that initiate the autoreactive process. We have developed a murine cytomegalovirus model of Sjogren's syndrome in which defects in the Fas/FasL pathway are necessary to enable chronic inflammation, even after the initial virus has been cleared. Another interaction between the endocrine system and apoptosis is by direct hormone interaction. This is exemplified by the orphan steroid receptor Nur77. Nur77 is important for T cell apoptosis after signaling through CD3. We have demonstrated that a dominant-negative Nur77 transgenic mouse exhibits a defect in thymic selection of T cells. Therefore, there are many potential mechanisms by which endocrine glands or hormones can affect the Fas apoptosis pathway, resulting in either cell death or a chronic inflammatory disease in the endocrine system, leading to hypothyroidism and diabetes. This inflammatory dysfunction can be reversed by a dominant-negative I kappa B that prevents nuclear translocation of NF-kappa B. We have developed antigen-specific, antigen-presenting cells that express high levels of FasL that can prevent **tissue-specific** inflammatory disease. Treatment with these cells prevents development of diabetes in NOD mice. Further understanding of the role and regulation of apoptosis in diseases of the endocrine system (e.g., diabetes, thyroiditis) should lead to better methods of treatment and prevention of these diseases.

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